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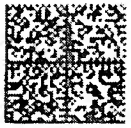

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,810	11/17/2003	Shengwen Li	ALLE0004-100 (17614(BOT))	5198

34132 7590 02/18/2005

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,810	LI ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-72 is/are pending in the application.

4a) Of the above claim(s) 3,4,12-17 and 22-72 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,5-11 and 18-21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11/17/03 &5/12/04 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/12/04.
4) ☑ Interview Summary (PTO-413) Paper No(s)/Mail Date. 12/1/04
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A preliminary amendment filed May 12, 2004 is acknowledged, where the original Figs. 1 and 2 were substituted.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1, 2, 5-11 and 18-21 during a telephone conversation with Quan Nguyen on December 14, 2004. Claims 3, 4, 12-17 and 22-72 are non-elected inventions and are withdrawn from consideration. Thus, claims 1, 2, 5-11 and 18-21 are examined.

Informalities

The disclosure is objected to because of the following informalities:

3. Fig. 2 is objected to because the drawing recites the peptide sequence of SEQ ID NO:5 being SEQ ID NO:39, which is not correct. Appropriate correction is required.

4. The specification recites amino acid and nucleotide sequences at pages 25 (e.g., tetrapeptides), 26, 37 and 38, however, there are no sequence identifiers "SEQ ID NO:" provided. Applicants must comply with the requirements of the sequence rules (37 CFR 1.821-1.825) and provide a new copy of sequence listing and CRF containing all the sequences.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 2, 20 and 21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 10 of U. S. Patent 6,203,794. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 2, 20 and 21 in the instant application disclose a method of treating a botulinum toxin intoxication in a mammal by administering an effective amount of a rescue agent such as the rescue agent comprising an inactive botulinum toxin. This is obvious in view of claim 10 in the patent which disclose a method for treating a mammal having acute botulinum poisoning comprising administering an effective amount of a solution comprising an inactive clostridial neurotoxin having an inactivated light chain and an unaltered heavy chain, and a drug joined to the inactive light chain of the inactive neurotoxin. The claims of the instant application and the claim of the patent are directed to a method of treating a botulinum toxin intoxication in a mammal by administering an effective amount of a rescue agent comprising an inactive botulinum toxin. Thus, claims 1, 2, 20 and 21 in present application and claim 10 in the patent are obvious variations of a method of treating a botulinum toxin intoxication in a mammal by administering an effective amount of a rescue agent comprising an inactive botulinum toxin.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2, 6-11 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 6-11 and 18-21 are directed to a method of treating a botulinum toxin intoxication in a mammal by administering an effective amount of a rescue agent such as the rescue agent comprising an inactive botulinum toxin. While the specification indicates the present invention provides for effective methods of treating botulinum intoxication comprising administering an effective amount of a rescue agent, where a rescue agent comprises at least one of inactive botulinum toxin (iBoNT), for example, a glycosylated iBoNT, which has a reduced antigenicity (paragraph [0027]), the specification does not disclose a genus of variants for a rescue agent or an inactive botulinum toxin in the method of treating a botulinum toxin intoxication in a mammal.

The specification indicates that a rescue agent comprises an iBoNT, which contains a heavy chain and a light chain, wherein the light chain is mutated as to have minimal or no ability to interfere with the release of neurotransmitters from a cell or a nerve end, e.g., iBoNT/A having the amino acid sequence of SEQ ID NO:4 (paragraph [0060]); the iBoNT, which is glycosylated, has reduced or no antigenicity (paragraphs [0061]-[00102]); and the use of g-iBoNT as antidote in accidental overdose in the treatment of postherpetic neuralgia (Example 8), or for detoxification (Example 9). However, the specification does not describe a genus of variants for

a rescue agent or an inactive botulinum toxin in the method of treating a botulinum toxin intoxication in a mammal. A single species of a rescue agent (e.g., iBoNT/A having the amino acid sequence of SEQ ID NO:4 (iBoNT/A-Hall (H227Y); Fig. 10) or the glycosylated thereof) do not provide original descriptive support for a genus of variants for a rescue agent or an inactive botulinum toxin. The variants of rescue agents do not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Applicants have described a specific inactive botulinum toxin (iBoNT/A-Hall (H227Y); Fig. 10) in the method of treating a botulinum toxin intoxication in a mammal, however, a genus of variants for a rescue agent or an inactive botulinum toxin have not been sufficiently described.

The skilled artisan cannot envision all the contemplated compounds based upon the general suggestion of a functional characteristic of a rescue agent or inactive botulinum toxin in the claimed method. The detailed structures must be taught, therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of preparation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30

USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF'S were found unpatentable due to lack of written description for the broad class.

Therefore, only those embodiments described and disclosed meet the written description requirement and not the full breadth of the claim meets the written description provision of 35 USC 1 12, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 2, 5-11 and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 5-11 and 18-21 are indefinite as to what effective amount of at least one rescue agent would do in the method treating a botulinum toxin intoxication. Claims 2, 5-11 and 18-21 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 20 and 21 are rejected under 35 U.S.C. 102(b) as anticipated by Dolly *et al.* (U.S. Patent 6,203,794, publication date: March 20, 2001).

Dolly *et al.* teach the use of an inactive clostridial neurotoxin in the preparation of a medicament for treating botulinum toxin poisoning, wherein the inactive clostridial neurotoxin (e.g., botulinum toxin A modified at His^{227} (to Tyr^{227}) or Glu^{224} (to Gln^{224})) can be used either alone or conjugation to another drug (e.g., Captopril or another zinc protease inhibitor), and wherein a therapeutically effective amount of the conjugate or inactive toxin is administered by intramuscular injection (column 2, lines 13-56; Example 18; column 36, lines 1-26; claims 1, 2, 20 and 21).

9. Claims 1, 20 and 21 are rejected under 35 U.S.C. 102(b) as anticipated by Lisk *et al.* (WO 2002/089834, publication date: November 14, 2002).

Lisk *et al.* teach a method of treating a patient with botulinum toxin A (BoNT/A) or botulinum toxin C1 (BoNT/C1) poisoning by administering botulinum toxin E (BoNT/E) or a fragment of synaptosomal-associated polypeptide of 25 kDa (SNAP-25) obtained by the cleavage of SNAP-25 with BoNT/E, wherein the toxin is administered by intramuscular injection (page 5, line 24-page 6, line 15; Example 1; page 18, line 13-page 19, line 5; page 33, lines 14-24; claims 1, 20 and 21).

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CMK
February 16, 2005

PTO/SB/08a (05-03)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 10

Complete if Known	
Application Number	10/715,810
Filing Date	November 17, 2003
First Named Inventor	Shengwen Li
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	ALLE0004-100 (17614(BOT))

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number - Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CMK	AA	US-6,458,365	10/01/2002	Aoki et al	
	AB	US- 5,766,605	06/16/1998	Sanders et al	
	AC	US- 5,714,468	02/03/1998	Dao	
	AD	US- 6,464,986	10/15/2002	Aoki et al	
	AE	US- 6,113,915	09/05/2000	Aoki et al	
	AF	US- 6,306,403	10/23/2001	Donovan	
	AG	US- 6,299,893	10/09/2001	Schwartz et al	
	AH	US- 5,670,484	09/23/1997	Binder	
	AI	US- 6,423,319	07/23/2002	Brooks et al	
	AJ	US- 6,139,845	10/31/2000	Donovan	
	AK	US- 6,143,308	11/07/2000	Donovan	
	AL	US- 5,437,291	08/01/1995	Pasricha et al	
	AM	US- 6,365,164	04/02/2002	Schmidt	
	AN	US- 6,063,768	05/16/2000	First	
	AO	US- 6,395,277	05/28/2002	Graham	
	AP	US- 6,265,379	07/24/2001	Donovan	
	AQ	US- 6,358,513	03/19/2002	Voet et al	
	AR	US- 6,328,977	12/11/2001	Donovan	
	AS	US- 6,306,423	10/23/2001	Donovan	
CMK	AT	US- 6,312,708	11/06/2001	Donovan	

FOREIGN PATENT DOCUMENTS

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CMK	EE	WO02/089834	11/04/02	Imperial College Inovations		

Examiner Signature		Date Considered	2/16/05

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Sheet 2 of 10

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CMK	EG	US-6,051,239	04/18/2000	Simpson et al	
CMK	EH	US- 6,203,794	03/20/2001	Dolly et al	
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OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
CMK	AU	PARK and SIMPSON, "Inhalational poisoning by botulinium toxin and inhalation vaccination with its heavy-chain component," Infect. Immun. (2003) 71:1147-1154.	
	AV	ATASSI and OSHIMA, "Structure, activity and immune (T and B cell) recognition of botulinum neurotoxins," Crit. Rev. Immunol. (1999) 19:219-260.	
	AW	MARCHESE RAGONA, et al., "Management of parotid sialocele with botulinum toxin," The Laryngoscope (1999) 109:1344-1346.	
	AX	WIEGAND, et al., "125-I labelled botulinum A neurotoxin: pharmacokinetics in cats after intramuscular injection," Naunyn-Schmiedeberg's Arch. Pharmacol. (1976) 292:161-165.	
	AY	HABERMANN, "125-I labeled neurotoxin from Clostridium botulinum A: preparation, binding to synaptosomes and ascent to the spinal cord," Naunyn-Schmiedeberg's Arch. Pharmacol. (1974) 281:47-58.	
	AZ	MOYER, et al., "Botulinum Toxin Type B: Experimental and Clinical Experience," In Therapy with Botlinum Toxin, Jankovic, ed., 1994, pp 71-84.	
	BA	GONELLE-GISPERT, "SNAP-25a and -25b isoforms are both expressed in insulin secreting cells and can function in insulin secretion," Biochem. J. (1999) 339:159-165.	
	BB	International Conference on Botulinum Toxin: Basic Science and Clinical Therapeutics," Mov. Disord. (1995) 10:381-408.	
	BC	HABERMAN, et al., "Tetanus toxin and botulinum A and C neurotoxins inhibit noradrenaline release from cultured mouse brain," J. Neurochem. (1988) 51:522-527.	
	BD	SANCHEZ-PRIETO, et al., "Botulinum toxin A blocks glutamate exocytosis from guinea pig cerebral cortical synaptosomes," Eur. J. Biochem. (1987) 165:675-681.	
CMK	BE	PEARCE, "Pharmacologic characterization of botulinum toxin for basic science and medicine," Toxicon (date) 35:1373-1412.	

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CMK	BF	BIGALKE, et al., "Botulinum A neurotoxin inhibits non-cholinergic synaptic transmission in mouse spinal cord neurons in culture," Brain Res. (1985) 360:318-324.	
	BG	HABERMANN, "Inhibition by tetanus and botulinum A toxin of the release of [3H] noradrenaline and [3H] GABA from rat brain homogenate," Experientia (1988) 44:224-226.	
	BH	BIGALKE, et al., "Tetanus toxin and botulinum A toxin inhibit release and uptake of various transmitters as studied with particulate preparations from rat brain and spinal cord," Naunyn-Schmiedelberg's Arch. Pharmacol. (1981) 316:244-251.	
	BI	JANCOVIC, et al., eds., "Therapy with Botulinum Toxin," New York, Marcel Dekkar, 1994. p.5.	
	BJ	SCHANTZ, et al., "Properties and use of botulinum toxin and other microbial neurotoxins in medicine," Microbial Rev. (1992) 56:80-99.	
	BK	SLOOP, et al., "Reconstituted botulinum toxin type A does not lose potency in humans if it is refrozen or refrigerated for two weeks before use," Neurology (1997) 48:249-253.	
	BL	GALBIATI, et al., "Identification, sequence and developmental expression of invertebrate flotillins from Drosophila melanogaster," Gene (1998) 210:229-237.	
	BM	LI, et al., "Src tyrosine kinases, Galpha subunits, and H-ras share a common membrane-anchored scaffolding protein, caveolin," J. Biol. Chem. (1996) 271:29182-29190.	
	BN	ISHIZAKA, et al., "Angiotensin II typpe receptor: Relationship with caveolae and caveolin after initial agonist simulation," Hypertension (1998) 32:459-466.	
	BO	JU, et al., "Inhibitory interactions of the bradykinin B2 receptor with endothelial nitric-acid synthase," J. Biol. Chem. (1998) 273:24025-24029.	
CMK	BP	WEBB, et al., "SR-BII, an isoform of the scavenger receptor BI containing an alternate cytoplasmic tail, mediates lipid transfer between high density lipoprotein and cells," J. Biol. Chem. (1998) 273:15241-15248.	

Examiner Signature		Date Considered	9/16/05

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 10

Complete if Known	
Application Number	10/715,810
Filing Date	November 17, 2003
First Named Inventor	Shengwin Li
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	ALLE0004-100 (17614(BOT))

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
CMK	BQ	DRAB, et al., "Loss of caveolae, vascular dysfunction, and priliminary defects in caveolin-1 gene-disrupted mice," Science (2001) 293:2449-2452.	
	BR	BOUILLOT, et al., "Axonal amyloid precursor protein expressed by neurons in vitro is present in a membrane fraction with caveolae-like properties," J. Biol. Chem. (1996) 271:7640-7644.	
	BS	RAZANI, et al., "Caveolae: From cell biology to animal physiology," Pharmacol. Rev. (2002) 54:431-467.	
	BT	LI, et al., "Phosphorylation of caveolin by src tyrosine kinases," J. Biol. Chem. (1996) 271:3863-3868.	
	BU	RAZANI and LISANTI, "Caveolin-deficient mice:insights into caveolar function and human disease," J. Clin. Investig. (2001) 108:1553-1561.	
	BV	GARCIA-CARDENA, et al., "Dissecting the interaction between nitric oxide synthase (NOS) and caveolin," J. Biol. Chem. (1997) 272:25437-25440.	
	BW	SOTGIA, et al., "Intracellular retention of glycophosphatidylinositol-linked proteins in caveolin-deficient cells," Mol. Cell. Biol. (2002) 22:3905-3926.	
	BX	FRANK, et al., "Influence of caveolin-1 on cellular cholesterol efflux mediated by high-density lipoproteins," Am. J. Physiol. Cell Physiol. (2001) 280:C1204-C1214.	
	BY	GALBIATI, et al., "Caveolin-1 expression negatively reguates cell cycle progression by inducing G0/G1 arrest via a p53/p21WAF1/Cip1-dependent mechanism," Mol. Biol. Cell. (2001) 12:2229-2244.	
	BZ	FRANK, et al., "Adenovirus-mediated expression of cavolin-1 in mouse liver increases plasma high-density lipoprotein levels," Biochemistry (2001) 40:10892-10900.	
CMK	CA	LEE, et al., "Src-induced phosphorylation of caveolin-2 on tyrosine 19," J. Biol. Chem. (2002) 277:34556-34567.	

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Sheet 6 of 10

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Filing Date	November 17, 2003
First Named Inventor	Shengwin Li
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
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CMK	CB	COUET, et al., "Identification of peptide and protein ligands for the caveolin-scaffolding domain," J. Biol. Chem. (1997) 272:6525-6533.	
	CC	LEE, et al., "Constitutive and growth factor-regulated phosphorylation of caveolin-1 ocurrs at the same site (Tyr-14) in vivo: identification of a c-src/cav-1/grb7 signalling cassette," Mol. Endocrinol. (2000) 14:1750-1775.	
	CD	SATO, et al., "Reconstitution of src-dependent phospholipase Cgamma phosphorylation and transient calcium release by using membrane rafts and cell-free extracts from Xenopus eggs," J. Biol. Chem (2003) 278:38413-38420.	
	CE	GARGALOVIC and DORY, "Cellular apoptosis is associated with increased caveolin-1 expression in macrophages," J. Lipid Res. (2003) 44:1622-1632	
	CF	HAMER, et al., "Rational design of drugs that induce human immunodeficiency virus replication," J. Virol. (2003) 77:10227-10236.	
	CG	McINTOSH, et al., "Targeting endothelium and its dynamic caveolae for tissue-specific transcytosis in vivo: a pathway to overcome cell barriers to drug and gene delivery," Proc. Natl. Acad. Sci. USA (2002) 99:1996-2001	
	CH	LI, et al., "Baculovirus-based expression of mammalian caveolin in Sf21 insect cells," J. Biol. Chem. (1996) 271:28647-28654.	
	CI	LI, et al., "Expression and characterization of recombinant caveolin," J. Biol. Chem. (1996) 271:568-573.	
	CJ	DOBROSOTSKAYA, et al., "Reconstitution of sterol-regulated endoplasmic reticulum-to-Golgi transport of SREBP-2 in insect cells by co-expression of mammalian SCAP and Insigs," J. Biol. Chem. (2003) 278:35837-35843.	
	CK	SCHNITZER, et al., "Endothelial caveolae have the molecular transport machinary for vesicle budding, docking, and fusion including VAMP, NSF, SNAP, annexins and GTPases," J. Biol. Chem. (1995) 270:14399-14404.	
CMK	CL	HAYASHI, et al., "Amyloid precursor protein in unique cholesterol-rich microdomains different from caveolae-like domains," Biochim. Biophys. Acta (2000) 1483:81-90.	

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Sheet 7 of 10

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Filing Date	November 17, 2003
First Named Inventor	Shengwin Li
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	ALLE0004-100 (17614(BOT))

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CMK	CM	BANWAIT, et al., "Role of nitric acid in beta(3)-adrenoreceptor activation on basal tone of internal anal sphincter," Am. J. Physiol.-Gastroint. Liver Physiol. (2003) 285:G547-G555.	
	CN	McLOON and CHRISTIANSEN, "Increasing extraocular muscle strength with insulin-like growth factor," Investig. Opthamol. Visual Sci. (2003) 44:3866-3872.	
	CO	CARVER and SCHNITZER, "Caveolae: mining little caves for new cancer targets," Nature Reviews Cancer (2003) 3:571-581.	
	CP	SCHNITZER, "Caveolae: from basic trafficking mechanisms to targeting transcytosis for tissue-specific drug and gene delivery in vivo," Adv. Drug. Deliv. Rev. (2001) 28:265-280.	
	CQ	McINTOSH and SCHNITZER, "Caveolae require intact VAMP for targeted transport in vascular endothelium," Am. J. Physiol. (1999) 277:H2222-H2232.	
	CR	LEE, et al., "Tumor cell growth inhibition by caveolin re-expression in human breast cancer cells," Oncogene (1998) 16:1391-1397.	
	CS	PAJVANI, et al., "Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications for metabolic regulation and bioactivity," J. Biol. Chem. (2003) 278:9073-9085.	
	CT	MYNARCIK, et al. "Adiponectin and leptin levels in HIV-infected subjects with insulin resistence and body fat redistribution," J. Acquir. Immun. Defic. Syndr. (2002) 31:514-520.	
	CU	RAJALA, et al., "Adipose-derived resistin and gut-derived resistin-like molecule-beta selectively impair insulin action on glucose production," J. Clin. Invest. (2003) 11:225-230.	
	CV	MENZAGHI, et al., "A haplotype at the adiponectin locus is associated with obesity and other features of the insulin resistence syndrome," Diabetes (2002) 51:2306-2312.	
CMK	CW	IYENGAR, et al., "Adipocyte-sereted factors synergistically promote mammary tumorigenesis through induction of anti-apoptotic transcriptional programs and proto-oncogene stabilization," Oncogene (2003) 22:6408-6423.	

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Sheet 8 of 10

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Examiner Name	Not Yet Assigned
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CMK	CX	COHEN, et al., "Role of caveolin and caveolae in insulin signaling and diabetes," Am. J. Physiol. Endocrinol. Metab. (2003) 285:E1151-E1160.	
	CY	KRATCHMAROVA, et al., "A proteomic approach for indentification of secreted proteins during the differentiation of 3T3-L1 preadipocytes to adipocytes," Mol. Cell. Proteomics (2002) 1:213-222.	
	CZ	COMBS, et al., "Induction of adipocyte complement-related protein of 30 kilodaltons by PPARgamma agonists: a potential mechanism of insulin sensitization," Endocrinology (2002) 143:998-1007.	
	DA	BERG, et al., "ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism," Trends Endocrinol. Metab. (2002) 13:84-89.	
	DB	COMBS, et al., "Endogenous glucose production is inhibited by the adipose-derived protein Acrp30," J. Clin. Invest. (2001) 108:1875-1881.	
	DC	RAZANI, et al., "Caveolin-1-deficient mice are lean, resistant to diet-inuced obesity, and show hypertriglyceridemia with adipocyte abnormalities," J. Biol. Chem. (2002) 277:8635-8647.	
	DD	SHIN, et al., "Involvement of cellular caveolae in bacterial entry into mast cells," Science (2000) 289:785-788.	
	DE	BURGUENO, et al., "Metabotropic glutamate type 1apipha receptor localizes in low-density caveolin-rish plasma membrane fractions," J. Neurochem. (2003) 86:785-791.	
	DF	TANG, et al., "Expression of metabotropic glutamate receptor 1alpha in the hippocampus of rat pilocarpine model of status epilepticus," Epilepsy Res. (2001) 46:179-189.	
	DG	CIRUELA, et al., "Motabotropic glutamate 1alpha and adenosine A1 receptors assemble into functionally interacting complexes," J. Biol. Chem. (2001) 276:18345-18351.	
CMK	DH	ZHANG, et al., "Localization and regulation of the delta-oplod receptor in dorsal root ganglia and spinal cord of the rat and monkey: evidence for association with the membrance of large dense-core vesicles," Neuroscience (1998) 82:1225-1242.	

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Sheet 9 of 10

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First Named Inventor	Shengwin Li
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	ALLE0004-100 (17614(BOT))

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CMK	DI	SKOFF, et al., "Nerve growth factor (NF) and glial cell line-derived neurotrophic factor (GDNF) regulate substance P release in adult spinal sensory neurons," Neurochem. Res. (2003) 28:847-854.	
	DJ	SCHAIBLE, et al., "Mechanisms of pain in arthritis," Ann. NY Acad. Sci. (2002) 966:343-354.	
	DK	XU, et al., "On the role of galanin, substance P and other neuropeptides in primary sensory neurons of the rat: studies on spinal reflex excitability and peripheral axotomy," Eur. J. Neurosci. (1990) 2:733-743.	
	DL	TREVISANI, et al., "Ethanol elicits and potentiates nociceptor responses via the vanilloid receptor," Nat. Neurosci. (2002) 5:546-551.	
	DM	MALCANGIO, et al., "A novel control mechanism based on GDNF modulation of somatostatin release from sensory neurones," FASEB J. (2002) 16:730-732.	
	DN	SOUTHALL, et al., "Twenty-four hour exposure to prostaglandin down regulates prostanoid receptor binding but does not alter PGE(2)-mediated sensitization or rat sensory neurons," Pain (2002) 98:285-296.	
	DO	MARVIZON, et al., "Neurokinin 1 receptor internalization in spinal cord slices induce by dorsal root stimulation is mediated by NMDA receptors," J. Neurosci. (1997) 17:8129-8136.	
	DP	MORIOKA, et al., "Interleukin-1beta-induced substance P release from rat cultured primary afferent neurons driven by two phospholipase A2 enzymes: secretory type IIA and cystolic type IV," J. Neurochem. (2002) 80:989-997.	
	DQ	ALLEN, et al., "Noxious cutaneous thermal stimuli induce a graded release of endogenous substance P in the spinal cord: imaging peptide action in vivo," J. Neurosci. (1997) 17:5921-5927.	
	DR	HARRIS, et al., "Expression of caveolin by bovine lymphocytes and antigen-presenting cells," Immunology (2002) 105:190-195.	
CMK	DS	SHIN and ABRAHAM, "Glycosylphosphatidylinositol-anchored receptor-mediated bacterial endocytosis," FEMS Microbiol. Lett. (2001) 197:131-138.	

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CHK	DT	FIELD, et al., "Fc epsilon RI-mediated recruitment of p53/56lyn to detergent resistent membrane domains accompnies cellular signalling," Proc. Natl. Acad. Sci. USA (1995) 92:9201-9205.	
	DU	BAIG, et al., "Agonist activated adrenocorticotropin receptor internalizes via a clathrin-mediated G protein receptor kinase dependent mechanism," Endocrin. Res. (2002) 28:281-289.	
	DV	KOHNO, et al., "N-glycans of sphingosine 1-phosphate receptor Edg-1 regulate ligand-induced receptor internalization," FASEB J. (2002) 16:983-992.	
	DW	DALE, et al., "Agonist-stimulated and tonic internalization of metabotropic glutamate receptor 1a in human embryonic kidney 293 cells: agonist-stimulated endocytosis is beta-arrestin 1 isoform-specific," Mol. Pharmacol. (2001) 60:1243-1253.	
	DX	OSTROM, et al., "Receptor number and caveolar co-localization determine receptor coupling efficiency to adenylyl cyclase," J. Biol. Chem. (2001) 276:42063-42069.	
	DY	OSTROM, et al., "Stoichiometry and compartmentation in G protein-coupled receptor signalling: implications for therapeutic interventions involving G(s)," J. Pharmacol. Exp. Ther. (2000) 294:407-412.	
	DZ	RIDDELL, et al., "Compartmentalization of beta-secretase (Asp20 into low-bouyant density, noncaveolar lipid rafts," Curr. Biol. (2001) 11:1288-1293.	
	EA	ROUVINSKI, et al., "Both raft- and non-raft proteins associate with CHAPS-insoluble complexes: some APP in large complexes," Biochem. Biophys. Res. Comm. (2003) 308:750-758.	
CHK	EB	IKEZU, et al., "Caveolae, plasma membrane microdomains for alpha-secretase-mediated processing of the amyloid secretory protein," J. Biol. Chem. (1998) 273:10485-10495.	

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Interview Summary	Application No.	Applicant(s)	
	10/715,810	BARRIER ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Chih-Min Kam*. (3)_____.

(2) *Quan Nguyen*. (4)_____.

Date of Interview: *14 December 2004*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Applicant elects with traverse of Group I, claims 1, 2, 5-11 and 18-21 regarding the restrcition requirement*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.